REMARKS/ARGUMENTS

Amendments to the Specification

The following amendments are made to the Specification in response to the Examiner's objections at paragraph 15 and 16, Applicants have provided several replacement paragraphs with the indicated amendments. No new matter has been added to the application.

In compliance with 37 CFR 1.121 the amendments made to the specification are presented by replacement paragraph. Each replacement paragraph is identified by its original paragraph number. Each amendment is made by underlining the added words or numbers, striking through the deleted words, or double bracketing of deleted numbers. Applicants respectfully request withdrawal of these objections.

Amendments to the Sequence Listing

The Examiner has maintained an objection to the Sequence Listing for omitting a sequence identifier for the amino acid sequence, EQKLISEEDL. The Examiner states that the revised Sequence Listing is not compliant with the sequence listing rules. Applicants have made revised the sequence listing to comply with the rules. The sequence listing is submitted with this amendment.

Amendments to the Claims

Claim 17 has been further amended to correct a typographical error "derivate" by replacing it with "derivative".

REJECTION OF CLAIMS 17 UNDER 35 USC 112, SECOND PARAGRAPH

Claim 17 was again rejected under 35 USC 112, second paragraph for recitation of "a derivative". The Examiner reasons that the term "derivative" encompasses any modification made to the antibody or fragment which include changes occurring in a CDR domain.

This rejection is respectfully traversed.

35 USC 112, second paragraph states "The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention."

In response to the previous Office Action, Applicants amended claim 17 to include " **having binding properties including ability to bind to its cognate ligand**". This language was as close to the language used by the Examiner as possible. Also, it would appear to show that any derivative has binding activity.

The present Office Action repeats the same rejection on the grounds that the derivative might not be functional if a modification of the CDR domain is present in the derivative. In an attempt to resolve this issue, Applicants have added the adjective "**functional**" to modify the antibody, the Fab, and their derivatives, although as far as Applicants can tell, the first amendment accomplished the same thing. Having made either of these amendments to claim 17, it should be clear to a person skilled in the art that claim 17 encompasses only functional molecules and not non-functional molecules. Applicant's use of the term "functional" should be read as clarifying the previous amendment. It is not intended to further limit the scope of the claim. Applicant's purpose in making this concession is only to reduce the number of issues in this application.

The Examiner finally states that "The specification does not demonstrate antibodies or fragments thereof with CDR modifications much less those retaining the ability to bind an antigen."

However, the MPEP at 2172 points out that "The content of applicant's specification is not used as evidence that the scope of the claims is inconsistent with the subject matter which applicants regard as their invention. As noted in *In re Ehrreich*, 590 F.2d 902, 200 USPQ 504 (CCPA 1979), agreement, or lack thereof, between the claims and the specification is properly considered only with respect to **35 U.S.C. 112**, first paragraph; it is irrelevant to compliance with the second paragraph of that section."

Rejection of Claims under 35 U.S.C. 102

The rejection of Claim 15 under 35 U.S.C. 102(a) as being anticipated by Francois et al. is maintained. The Examiner has maintained the rejection over Francois et al. pointing out that the features upon which Applicants rely are not stated in Claim 15.

Francois et al makes a polyprotein expression cassette that expresses a polyprotein. A polyprotein is an artificial construct made up of two or more proteins separated by a linker. In the case of Francois et al, the cleavable chimeric polyprotein consisted of a first antimicrobial protein, DmAMP1 from *Dahlia merckii* seeds and a second antimicrobial protein, RsAFP2 from *Raphanus sativus* seeds. The end products of Francois et al are two separate proteins. The end product of claim 15 is a multimeric protein. Instead of the individual proteins going their separate ways as in Francois et al, the proteins of the present invention stay together to form a conformational multimeric protein.

1. The present invention is a method of making a multimeric protein. Francois et al make a polyprotein. This method cannot anticipate the present invention because the process this reference teaches does not result in a multimeric protein.

2. The present invention uses a propeptide with functionality different from the propeptide/linker peptide of Francois et al.. A propeptide of claim 15 is a peptide that occurs between two peptides of interest in a proprotein, and assists in forming a conformational and proximational association between the two peptides of interest, which results in a stable intermediate. The two peptides of interest then form a multimeric protein. Therefore, the propeptide is not a merely a linker peptide in the sense that Francois et al use the term. A discussion of the propeptide and its release can be found at paragraphs 11, 12, 19, 20, 130, 502 and 550.

3. Applicants have amended Claim 15 to recite, "**wherein the signal peptide and the propeptide are released**". This is intended to address the concerns of the Examiner. The Examiner's further comment about Claim 17 is not understood in the present context.

Accordingly, applicants respectfully request that the Examiner reconsider and modify or withdraw this ground of rejection.

Claims 15, 17 are rejected under 35 U.S.C. 102(a) as being anticipated by Wu et al. Applicants respectfully traverse this rejection.

Applicants respectfully traverse this rejection. Wu et al has two characteristics that differentiate it from the present invention. 1. The linker does not guide the conformational assembly of the desired product. If the linker could guide conformational assembly, then it would have been designed to avoid cross-assembly of the variable regions. The linker's function is merely to link two parts of the single-chain-antibody. . "Thus, domain exchange or cross-pairing appears to be the basis of the observed multimerization." 2. The linker remains in place. It is not removed by cellular mechanisms. These are reasons why a propeptide is not simply referred to referred to as a linker. Wu makes a "single-chain antibody" which can cross pair to form a diabody. Wu et al apparently thought that the multimers were the product of "misassembly" wherein a variable region of one single-chain interacts with a variable region of another single chain. Their use of the term "misassembly" as the cause of multimerization clearly indicates that the outcome was undesirable.

The propeptide of the present invention is free of the problems of Wu et al, and has functions that are not properties of a linker. In the present invention, the propeptide has a **chaperonin-like function**, guiding the conformational assembly of the proprotein to achieve proper assembly (or avoid "misassembly"). After correct conformational assembly has been achieved, the propeptide is no longer needed. The propeptide is **then removed** by cellular mechanisms. This removal is not only different from the outcome of Wu et al, it is also different from enzymatic or chemical cleavage of a linker. In the present invention there is no residual chain of amino acids. A left over chain of amino acids would potentially alter the specificity and/or the binding strength of single-chain-antibody, or of an immunoglobulin product..

For these reasons, Claim 15, and 17 are not anticipated by Wu et al. and would not be obvious over Wu et al or Wu et al in combination with other references that have been cited. Accordingly, Applicants respectfully request reconsideration, and either modification or withdrawal of this ground of rejection.

Rejection of Claims under 35 U.S.C. 103

Claims 15-17 are rejected under 35 U.S.C. 103(a) over Cabilly, Jostick and Sawai and Inoue.

Claim 17 as Currently Amended recites a method of making an antibody, derivative of an antibody, a Fab fragment, a derivative of a Fab fragment. Claim 17 defines each as a multimeric protein derivative having binding properties including ability to bind to its cognate ligand.

Steps a, b, c, and d of claim 15 set forth a method of making a single continuous gene that encodes an entire multimeric protein; such as an antibody, derivative of an antibody, a Fab fragment, a derivative of a Fab fragment.

Cabilly does not qualify as prior art, because it requires two independently expressed genes to make an immunoglobulin or immunoglobulin fragment. Claim 1 of Cabilly states

> "A process for producing **an immunoglobulin** molecule **or** an immunologically functional
>
> **immunoglobulin fragment** comprising at least the variable domains of the immunoglobulin heavy and light chains, in a single host cell, comprising the steps of: (i) transforming said single host cell with a **first DNA sequence encoding** at least the variable domain of **the immunoglobulin heavy chain** and **a second DNA sequence encoding** at least the variable domain of **the immunoglobulin light chain**, and (ii) **independently expressing said first DNA sequence and said second DNA sequence** so that said immunoglobulin heavy and light chains are produced as separate molecules in said transformed single host cell."

The present invention requires expression of a single gene to make an immunoglobulin. Cabilly and all other methods require two separately expressed genes, whether expressed in animal cells or plant cells. The present invention is therefore non-obvious in view of any set of references combined with Cabilly. Accordingly, applicants request reconsideration, modification or withdrawal of this ground of rejection.

Applicants invention does not use a linker arrangement and does not produce a single-chain antibody arrangement. Jostick and Inuoe use linker arrangements in contrast to the propeptide used by applicants.

No Suggestion to Combine references/No combination that makes the present invention

Cabilly and Sawai cannot validly be combined with Jostick and Inoue to suggest applicants invention. There is no suggestion stated or implied in any of the four references by which to combine them for any purpose. The use of a linker arrangement is antithetical to the assemblies of Cabilly, Sawai, or the presently claimed invention. An immunoglobulin or a Fab fragment does not require or use a linker arrangement. The parts of an immunoglobulin have a different method of getting together and remaining together that is not analogous to a string of extra amino acids. The fact that a linker may be dissected by a cleavage site does not turn a linker into a propeptide. The linker parts remain and are capable of altering the specificity and/or binding capacity of the immunoglobulin.

According to the present invention, a propeptide such as the insulin C chain or *Saccharmyces cerevisiae* K1 killer toxin propeptide is used. In each case the first and second peptide associate to assume a biologically functional conformation free of the propeptide. The design of an artificial proprotein is based on the observation that multimeric proteins often have a requirement for involvement of folding chaperones to complete their complex folding and assembly requirements. Proproteins are designed to comprise a molecular chaperon in the form of a propeptide to facilitate the proper folding of multimeric proteins. The propeptide influences the spatial distribution of the subunits by bringing them into close proximity. The creation of a proprotein by fusing the subunit polypeptides to a stable folding and conformational propeptide which is removed by cellular mechanisms results in proper subunit interactions without being resident in the mature protein. See specification paragraphs 131-138.

As pointed out above, a linker, even a cleavable linker only holds two peptides in close proximity. A cleavable linker is not intended to be removed. It is simply cleavable. Two strings of amino acids are left behind after cleavage to affect the functioning or even the proper alignment of the resulting protein.

Claims 15 and 17 were rejected under 35 U.S.C. 112, first paragraph, as being indefinite.

The Examiner states that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to make or use the invention. As desired by the Examiner, Applicants have included a promoter in claim 15, and mention of a disulfide bond in claim 17. Promoters and their uses are discussed extensively throughout the specification. Disulfide bonds are also widely mentioned throughout the specification. Accordingly, Applicants respectfully request that these grounds of rejection be reconsidered and withdrawn.

In light of the above amendments and remarks, Applicants believe that the application is in condition for allowance. Any fees required in addition to those mentioned specifically above may be charged to deposit account 500933.

Respectfully submitted,

Dated: April 23,2007 By: ___/Thomas Gallegos/___
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Attachments:

- Petition for a One Month Extension of Time to Reply
- Replacement Sequence Listing

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